REMARKS

Administrative Overview

Claims 1-19 are pending with claims 1, 6, 14, and 18 being the independent claims. Claims 1-19 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Vandeginste et al. ("Multicomponent Self-Modeling Curve Resolution in High-Performance Liquid Chromatography by Iterative Target Transformation Analysis," Analytical Chemica Acta, vol 173, pps 253-264 (1985)) (hereafter "Vandeginste") and claims 1-17 rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Hamilton et al. ("Mixture Analysis using Factor Analysis. II: Self-Modeling Curve Resolution," J. Chemometrics, vol 4, pp 1-13 (1990)) (hereafter "Hamilton"). Applicants respectfully disagree with the rejections alleged in the Office action.

Overview of Prior Art References

Vandeginste relates to iterative target transformation factor analysis using a total-component chromatogram. Accordingly, Vandeginste is only concerned with the analysis of a ***single*** spectrochromatogram. In Vandeginste, the ***one total-component chromatogram*** is obtained with respect to a mixture of eluting compounds ***during one experiment*** and then the single spectrochromatogram is analyzed iteratively based on an algorithm. The analytic approach of Vandeginste never uses a plurality of spectrochromatograms of the same mixture. Further, different experimental conditions are not applied to the same mixture. Thus, Vandeginste does not perform component matching using different chromatograms obtained under different chromatographic conditions.

In Hamilton, a large number of works on Multivariate (or Self-Modeling) Curve Resolution (MCR) techniques are reviewed. MCR is a method of extracting physically meaningful curves from a two-dimensional dataset. The MCR approaches of Hamilton are not concerned with and fail to describe component (chromatographic peak) matching. Further, the determination of a component's retention times in different chromatograms are not described in Hamilton. Instead, MCR is focused on the problem of profile extraction with respect to a ***single data set.*** Hamilton only describes a mathematical method "to determine the number of components in *an overlapped chromatographic* ..." and not all of the elements claimed. See, e.g., Hamilton, p 1. (Emphasis added by Applicants)

Applicants submit that based on the remarks provided below neither Vandeginste nor Hamilton teach each element of the claimed invention. Accordingly, each reference fails to anticipate the claimed invention.

Response to Rejections

Rejection of Claim 1 Under 35 U.S.C. § 102(b)

With respect to the rejection of claim 1 under 35 USC 102(b), claim 1 recites as follows:

> A method of characterizing a mixture of components, the method comprising the steps of:
> obtaining ***a plurality of spectrochromatograms of the mixture of components***, each of the spectrochromatograms being obtained under ***a respective one of a plurality of different chromatographic conditions***;
> estimating the number of components and
> performing component matching upon the ***spectrochromatograms*** using the estimated number of components. (emphasis added)

As mentioned above, Vandeginste relates to the analysis of a *single* spectrochromatogram. In contrast, the claimed method requires "*a plurality of spectrochromatograms of the mixture of components.*" This plurality of spectrochromatograms is for the *same mixture of components* such that each spectrochromatogram is obtained under "*a respective one of a plurality of different chromatographic conditions*." Further, the performance of "component matching upon the *spectrochromatograms*" also requires multiple *spectrochromatograms*. All of these elements and clauses are not described in Vandeginste. Thus, Vandeginste fails to teach all of the requirements of claim 1.

As discussed above, Hamilton's paper is a review of methods of data analysis known as Multivariate Curve Resolution (MCR). MCR does not solve the problem of mixture component matching between different chromatographic runs. Instead, MCR is a method of extracting curve shapes. Unlike the methods claimed, Hamilton only applies to a *single dataset of overlapping curve data*. That is, like Vandeginste, Hamilton is also limited to the analysis of a single spectrochromatogram such that component matching between spectrochromatograms, as claimed, is not a part of the description of Hamilton. This follows, in part, because MCR does not use a series of spectrochromatograms obtained under different chromatographic conditions as

claimed. Thus, as is the case with the elements of claim 1 recited above with respect to Vandeginste, Hamilton also fails to teach all of the requirements of claim 1.

As recited in some of the claimed embodiments, prior to performing an analysis, data sets are constructed by performing at least two experiments on a mixed sample, each experiment performed under a respective chromatographic condition. Thus, in contrast to the prior art of record, which only performs an analysis with respect to one data set associated with one chromatography experiment, the claimed invention is able to relate different chromatography experiments performed under different respective conductions to generate useful data relating to a mixture of components.

Neither Vandeginste nor Hamilton teaches the step of collecting spectrochromatographic data that is required in Applicants' claimed method such that component matching is performed upon the spectrochromatograms. As discussed above, prior to performing an analysis, embodiments of the claimed invention require performing a plurality of chromatographic experiments, each experiment is conducted at a different experimental condition. That is, the mixture is subjected to different respective chromatographic conditions as claimed. Some of the different conditions can include, but are not limited to, column type, column length, column diameter, column temperature, column particle size, the dead time of the system, pH of the buffer, solvent data (e.g., mobile phase, buffers, and gradient program), flow rate, and any combination thereof. See, e.g., Specification, paragraph 58. In contrast, neither Vandeginste nor Hamilton teaches any analytical experiments that precedes their analysis, but only describe mathematical methods without varying chromatographic conditions associated with a single mixture as claimed. In general, Hamilton fails to teach component matching as claimed.

As a result, Applicants respectfully submit that neither Vandeginste nor Hamilton teaches each element of Applicant's claimed invention. Specifically, the steps of obtaining a plurality of spectrochromatograms of the mixture of the components, each of the spectrochromatograms being obtained under a respective one of a plurality of different chromatographic conditions, and performing component matching using the spectrochromatograms, are not taught in either reference as recited in claim 1.

Accordingly, Applicants submit that claim 1 is not anticipated and is therefore patentable over the prior art of record. Applicant further submits that claims 2-5 are also patentable as depending from a patentable base claim.

Rejection of Claim 6 Under 35 U.S.C. § 102(b)

With respect to the rejection of claim 6 under 35 USC 102(b), claim 1 recites as follows:

A method of component peak matching comprising the steps of:
obtaining ***a plurality of spectrochromatographic data sets for a mixture of*** components, each spectrochromatographic data set comprising spectrochromatographic data;
creating an ***augmented spectrochromatographic data*** set by merging the spectrochromatographic data sets into a matrix;
determining a ***preliminary estimate of the number of components (n)*** in the augmented spectrochromatographic data set;
selecting the (n) most orthogonal spectrochromatographic data from the augmented spectrochromatographic data set;
generating a refined key spectra set; and
determining the component retention times. (emphasis added)

Applicants submit that to the extent claims 1 and 6 recite any of the same elements, that the arguments advanced with respect to claim 1 also apply to render claim 6 patentable over the prior art. Specifically, claim 6 recites the step of obtaining a plurality of spectrochromatograms of the mixture of the components, each of the spectrochromatograms being obtained under a respective one of a plurality of different chromatographic conditions and performing component matching using the spectrochromatograms. Since these elements are not taught in either Vandeginste or Hamilton, Applicants submit that claim 6 is not anticipated by either reference and should be passed to allowance.

Further, embodiments of the invention, such as claim 6, relate to characterizing a mixture of chemical compounds by n-Dimensional Mutual Automated Peak-Matching Chromatography. With respect to claim 6, a method of component peak matching is recited that requires the creation of an augmented data set, that includes a plurality of data sets. An augmented data set can include data sets obtained in at least two chromatographic experiments using different experimental conditions to yield two or more spectrochromatograms. Vandeginste does not create an augmented data set, i.e. merging the plurality of spectrochromatograms into a single data set. This follows for the simple reason that any such merging of data sets to create an augmented data set is not applicable in the case of single spectrochromatogram analysis described in Vandeginste. Specifically, Vandeginste performs the estimation of the number of

components (n) based on the analysis of a single spectrochromatogram, not the augmented data set recited in and required by claim 6.

In further detail, neither Vandeginste nor Hamilton teaches the step of creating an augmented data set by combining multiple data sets, each obtained in a High-Performance Liquid Chromatography (HPLC) experiment using different chromatographic conditions. For example, as shown in the Specification, Paragraph 87, of the application as filed, this invention illustrates the construction of the augmented data set by the following equation.

$$D_{aug} = [D_1\ D_2\ \ldots\ldots\ D_k] \qquad \text{(Eq. 1)}$$

where each of D_1, D_2, ... D_k is a data matrix obtained in an individual HPLC experiment. In addition, in the exemplary augmented data set, the column axis is the spectral axis and the row axis is the time axis. Accordingly, this exemplary augmented data set contains spectra information of *all* of the components in the mixture (whether co-eluting or well resolved) obtained under all of the HPLC experiments.

Vandeginste does not use the combination data set recited in claim 6, but instead teaches using "a (NS x NW) data matrix D of NS spectra measured at NW wavelengths" obtained in ***one*** HPLC experiment without varying chromatographic conditions. See, e.g., Vandeginste, pages 254-255. In addition, the data set in Vandeginste only contains information where two or more components co-elute in *one* HPLC experiment. None of the peaks that are resolved in the HPLC experiment of Vandeginste will be taken into consideration. Thus, no peak matching is performed in Vandeginste.

In addition, in contrast to Vandeginste, in claim 6 "n" is a preliminary estimate of the number of components, which is not the case in the method by Vandeginste, since no subsequent refinement is performed with other spectrochromatography. Vandeginste does not teach selecting a set of n of the most orthogonal spectra (the key set) from the augmented dataset, instead, the reference applies the rotation of PCA-determined eigenvectors. This is a very different approach. Subsequently, Vandeginste does not teach generating a refined key set. Further, Vandeginste does not teach determining explicitly the retention times of the components.

With respect to Hamilton, Applicants submit that none of MCR methods reviewed in the paper by Hamilton applies the above combination of all of the steps recited in claim 6. The refined key set spectra set selection procedure is unique to the Applicants claimed method. In

more detail, Applicants further submit that neither Vandeginste nor Hamilton anticipates Applicant's claimed methods because neither prior art teaches a method based on a key data set as required in claim 6. Claim 6 requires selecting the key data set (n) that is most orthogonal from the augmented spectrochromatographic data set and generating a refined key data set. Neither Vandeginste nor Hamilton teaches the selection of the key data set, but describes how to rotate the eigenvectors, generated in a principal component analysis, in such a way to produce estimates of the spectra and concentrations of the pure component. "The 'art' in SMCR is to find the correct or 'best' rotation of the eigenvectors," not to select and refine the key data set.

Accordingly, Applicants submit that claim 6 is not anticipated and is therefore patentable over the prior art of record. Applicant further submits that claims 7-13 are also patentable as depending from a patentable base claim.

Rejection of Claim 14 Under 35 U.S.C. § 102(b)

With respect to the rejection of claim 14 under 35 USC 102(b), claim 14 recites as follows:

A method for resolving a mixed sample of chromatographic components, the method comprising the steps of:

selecting ***a plurality of differing chromatographic conditions***;
performing a plurality of chromatographic runs on the mixed sample, each respective run performed under ***a respective chromatographic condition***;
obtaining spectrochromatographic data for the mixed sample during each of the chromatographic runs;
creating an ***augmented data set*** from the spectrochromatographic data of the plurality of chromatographic runs;
operating on the augmented data set to ***determine the retention times for each component in the mixed sample***; and
resolving each of the components.

Vandeginste and Hamilton fail to a describe the steps of selecting a plurality of differing chromatographic conditions; performing ***a plurality of chromatographic runs*** on the mixed sample, ***each respective run performed under a respective chromatographic condition***; obtaining spectrochromatographic data for the mixed sample during each of the chromatographic runs; ***creating an augmented data set*** from the spectrochromatographic data of the plurality of chromatographic runs; operating on the augmented data set to ***determine the retention times*** for

each component in the mixed sample. Thus, claim 14 is patentable for many of the same reasons claim 6 is patentable with respect to the prior art of record.

Further, neither Vandeginste nor Hamilton teach the component matching techniques claimed. As recited in claim 14, the claimed invention relates to the determination of the *retention time* of each component in the mixture in each spectrochromatogram. In comparison, neither Vandeginste nor Hamilton uses *retention time* as a factor in their respective analysis. Instead, the references teach resolving chromatographic elution profiles using criteria such as regression coefficients.

Accordingly, Applicants submit that claim 14 is not anticipated and is therefore patentable over the prior art of record. Applicant further submits that claims 15-17 are also patentable as depending from a patentable base claim.

Rejection of Claim 18 Under 35 U.S.C. § 102(b)

With respect to the rejection of claim 18 under 35 USC 102(b), claim 18 recites as follows:

> A method of obtaining the shape of components from spectrochromatographic data comprising the steps of:
> determining the number of components (n) and each component's retention time;
> generating uniqueness vectors as initial estimates of spectrochromatographic profiles; and
> performing profile resolution on the spectrochromatographic data.

Applicants submit that Vandeginste not only fails to anticipate claim 18, but actually teaches away from the approach claimed. Specifically, Applicants note that Vandeginste acknowledges the insufficient performance of his method when the spectral intensity of components differs significantly, e.g. 25:1 (p.264). The method recited in claim 18 is able to handle this problematic situation identified by Vandeginste.

A key differentiating point between the method of claim 18 relative to that of Vandeginste lies in the initial determination of component retention times from a plurality of spectrochromatograms of the same mixture obtained at different chromatographic conditions to generate initial estimates for use in later steps. Therefore, the claimed method is applicable to a

plurality of spectrochromatograms although able to resolve spectra and profiles in an individual dataset. The use of "initial estimates" of profiles for peak matching across multiple spectrochromatographic profiles as claimed leads to a better performance of the method. This limitations are not taught in either of the cited references.

Further, claim 18 comprises the step of determining the number of components (n) and each component's retention time. Based on the discussion above, neither Vandeginste nor Hamilton teach any of the above steps nor do they determine retention time.

Accordingly, Applicants submit that claim 18 is not anticipated and is therefore patentable over the prior art of record. Applicant further submits that claim 19 is also patentable as depending from a patentable base claim.

Therefore, Applicants submit that the pending independent claims and dependent claims dependent therefrom are patentable over Vandeginste and Hamilton and respectfully request reconsideration and withdrawal of the rejections.

CONCLUSION

Applicants submit that on the basis of the foregoing claim amendments, claims 1-19 are in condition for allowance. Should any further issues of anticipation or patentability be determined to exist, the Examiner is invited to contact the undersigned by telephone to expedite the favorable prosecution of this application.

In light of the foregoing, we submit that all claims are now in condition for allowance.

Respectfully submitted,

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